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EXAMINER

EPPERSON, JON D

ART UNIT	PAPER NUMBER
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1639

MAIL DATE	DELIVERY MODE
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05/17/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/052,942	<b>Applicant(s)</b> ZAUDERER ET AL.	
	<b>Examiner</b> Jon D. Epperson	<b>Art Unit</b> 1639	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 February 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-45 and 48-65 is/are pending in the application.
- 4a) Of the above claim(s) 37, 45, 48-52 and 58 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-36, 38-44, 53-57 and 59-65 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>2/15/07</u> | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Request for Continued Examination (RCE)***

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/15/07 has been entered. Claims 1-45 and 48-65 were pending. No claims were added, canceled, or amended. Therefore, claims 1-45 and 48-65 are still pending. Claims 37, 45, 48-52, and 58 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 1-36, 38-44, 53-57, and 59-65 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

### ***IDS***

2. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action (e.g., 2/15/07).

### **Withdrawn Objections/Rejections**

3. All rejections are maintained and the arguments are addressed below.

### **Outstanding Objections and/or Rejections**

#### ***Claim Rejections - 35 USC § 103***

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4. Claims 1, 9-19, 21, 24-32, 38-41, 53-57, and 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) in view of Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266) (of record) as evidenced by International Committee on Taxonomy of Viruses. ICTVdb Descriptions: 58. Poxviridae. Retrieved April 18, 2006, pages 1-3 and Wikipedia, the Free Encyclopedia. Poxviridae. Retrieved April 18, 2006, pages 1 and 2.

For *claim 1*, Marasco et al. (see entire document) disclose a method of selecting polynucleotides which encode an intracellular immunoglobulin molecule, or fragment thereof, including a single-chain immunoglobulin whose expression induces a modified phenotype in a eukaryotic host cell (see Marasco et al., abstract; see also column 37, lines 37-60; see also column 9, lines 32-37; see also column 31 and 32 disclosing the synthesis and screening of mutant libraries of intracellular immunoglobulin fragments; see especially column 31, lines 48-52), which reads on the claimed invention. For example, Marasco et al. (a) disclose providing a population of host cells capable of expressing said intracellular immunoglobulin molecule, or fragment thereof, wherein individual host cells of said population can be induced to exhibit a predetermined modified phenotype, wherein said modified phenotype is induced to via binding of said intracellular immunoglobulin molecule or fragment thereof to an intracellular antigen (e.g., see figure 3; see also columns 35 and 36, section entitled "Ability of Antibody Envelope Glycoprotein to Inhibit Envelope Protein Biosynthesis And Activity" starting on line 16

of column 34 disclosing a modified phenotype, decreased envelope protein biosynthesis, that occurs when the intracellular antibody, sFv105 or sFv105-KDEL, binds to the gp160 antigen in COS cells; see also column 8, paragraph 1, "the method of using intracellular antibodies to bind to the newly synthesized gp160 in the lumen of the endoplasmic reticulum and inhibit its transport to the Golgi apparatus, greatly reduces the amount of protein available for cleavage to gp120 and gp41. Accordingly, the viral particles produced have greatly diminished amounts of gp120 and gp41 on their surface. Such particles are not considered as infectious"; see also column 35, last paragraph, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited ... [wherein] sFv105-KDEL specific binding to the HIV-1 glycoprotein"; see also column 34, "Ability of Antibodies to be Expressed in Mammalian Cells" section; see also column 23, lines 13-17). Thus, the intracellular antibody, sFv105, induces a modified phenotype, change in gp120 biosynthesis and particle infectivity, by binding to an intracellular antigen, gp160. Marasco et al. also disclose **(b-c)** introducing into said population of host cells a first/second library of polynucleotides encoding, through operable association with a transcriptional control region, a plurality of first intracellular immunoglobulin subunit polypeptides, each comprising a first immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region and wherein said second intracellular immunoglobulin subunit polypeptides combine with said first intracellular immunoglobulin subunit polypeptides to form a plurality of intracellular immunoglobulin molecules (e.g., see paragraph bridging columns 11 and 12, "In one preferred embodiment, the genes encoding the light chain and heavy chain

encode a linker to make a single chain antibody (sFv) ... The sFv typically comprises a single peptide with the sequence  $V_H$ -linker- $V_L$  or  $V_L$ -linker- $V_H$  [Please note that this is being interpreted as an antibody "fragment" e.g., see specification, page 26, paragraph 68, "The single-chain fragment may comprise a single polypeptide with the sequence  $V_H$ -linker- $V_L$  or  $V_L$ -linker- $V_H$ "]. The linker is chosen to permit the heavy chain and light chain to bind together in their proper conformational orientation"; see also column 30, Construction and Expression of Mutant Antibodies section starting at line 46, "Using any of these broadly neutralizing antibodies, mutant antibodies [i.e., a library] can be generated can be generated. One can use standard mutagenesis techniques to result in cDNA coding for different amino acids in the variable regions of the heavy chain such as the CDR3 region [i.e., a library of heavy chain variable regions]"; see also column 31, lines 44-50; see also column 21, paragraph 2, "gene for the antibody can encompass ... the heavy chain and light chain regions. In addition, the gene is operably linked to a promoter"). Marasco also disclose (d) permitting expression of said plurality of intracellular immunoglobulin molecules, or fragments thereof in said population of host cells under conditions wherein said modified phenotype can be detected" (e.g., see "Ability of Antibody To Envelope Glycoprotein To Inhibit Envelope Protein Biosynthesis And Activity" section starting on line 14 of column 35; see also column 23, lines 13-17; see also "Inhibition of Function By Intracellular Antibody" section starting on column 4, line 9; see especially paragraph bridging columns 35 and 36, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited"). Thus, the expression of sFv105 intracellular antibodies results in a detectable change in phenotype

with regard to the processing of gp160. Finally, Marasco also disclose (c) recovering polynucleotides of said first library from those individual host cells which exhibit said modified phenotype (e.g., see column 31, lines 44-50, "Using the above-described technique, six mutant sFv105 antibodies were produced in which the amino acids in the CDR3 region of the heavy chain were replaced by random amino acids. One of the six mutants [recovered] designated R had a CDR3 region which coded for (SEQ ID NO:74)" see column 6, lines 29-34, "These antibodies can be produced and/or screened by standard techniques"; see also column 11, paragraph 2, "Thus, one can readily screen an antibody to insure that it has a sufficient binding affinity for the antigen"; see also column 12, lines 3-5, "then with phage display vectors pull out [i.e., recover] the antibodies with the different linkers and screen for the highest affinity single chain antibody generated"; see also column 13, lines 6 and 7, "One then screens the antibodies by standard techniques to find [i.e., recover] antibodies of interest"; see also column 24, lines 6 and 7, "One then screens the antibodies by standard techniques to find [i.e., recover] antibodies of interest").

For *claim 9*, Marasco et al. disclose human antibodies (e.g., see column 21, line 36; see also column 22, line 11; see also column 27, line 45; see also column 28, paragraph 1).

For *claims 10-17*, Marasco et al. disclose both heavy and light constant/variable regions (e.g., see column 21, paragraph 2, "gene for the antibody can encompass ... the heavy chain and light chain regions"; see also column 11, last two paragraphs; see also figures 1 and 2; see also column 30, paragraphs 1 and 2; see also column 31, last

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paragraph; see also column 33, paragraphs 1 and 2; see also column 11, line 31, which discloses “FAB” fragments, which contain both constant and variable regions; see also column 19, lines 11 and 12, “Once obtained, the V<sub>H</sub> and V<sub>L</sub> domains can be used to construct sFv, Fv or Fab fragments).

For *claims 18, 19, 24--32, 38, 39*, Marasco et al. disclose the “eukaryotic” poxvirus vector (e.g., see column 26, lines 43-46, “Other mammalian expression vectors such as herpes virus expression vectors, or pox virus expression vectors can also be used”; see also column 21, paragraph 3; see also column 25, last paragraph wherein RNA vectors are disclosed; see also column 18, lines 34 and 35 disclosing expression in the cytoplasm). Marasco et al. do not explicitly state that the vaccinia virus is a linear, double-stranded DNA vector. However, the Examiner contends that these would be inherent features of the virus as disclosed by the International Committee on Taxonomy of Viruses (e.g., see International Committee on Taxonomy of Viruses. ICTVdb Descriptions: 58. Poxviridae. Retrieved April 18, 2006, pages 1-3, see especially page 2, Nucleic Acid section, “Virions contain one molecule of linear double stranded DNA”). “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Furthermore, although Marasco et al. do not explicitly recite any of the poxvirus



in claim genera in claim 32, the Examiner contends that these classification would be immediately envisioned as the poxvirus only contain only 11 different members (e.g., see Wikipedia, the Free Encyclopedia. Poxviridae. Retrieved April 18, 2006, pages 1 and 2) in accordance with *In re Schauman*. When the reference teaches a small genus which places a claimed species in the possession of the public as in *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), and the species would have been obvious even if the genus were not sufficiently small to justify a rejection under 35 U.S.C. § 102. See MPEP § § 2131.02 and 2144.08 for more information on anticipation and obviousness of species by a disclosure of a genus.

For **claim 21**, Marasco et al. also disclose the use of a plasmid vector (e.g., see column 31, last paragraph; see also figure 3).

For **claims 40 and 41**, Marasco et al. disclose various promoters including constitutive promoters (e.g., column 21, paragraphs 1 and 2).

For **claims 53-57**, Marasco et al. disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen (e.g., see Marasco et al., page 9, second to last paragraph, “intracellular expression of an antibody to its target, for example, the antibody to the [HIV] envelope glycoprotein ... results in an antibody that binds the target, e.g. envelope glycoprotein ... and prevents further processing ... One could even have the antibody under the control of a promoter that will be specifically activated by the target (e.g. an HIV LTR) thereby only turning the antibody on when the target is present”; see also page 8, paragraph 3, “Syncytium

formation is mediated solely by the HIV-1 envelope protein expressed on the infected cell surface”; see also paragraph bridging pages 37-39 and figures 9-12). Marasco et al. disclose an altered susceptibility to HIV infection (e.g., see column 23, paragraph 2).

For *claims 59-62*, Marasco et al. disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence (e.g., see column 16, last paragraph wherein localization sequences are disclosed; see also column 33, line 40; see also column 13, line 40 wherein KDEL is disclosed). Furthermore, Marasco teach localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody (e.g., see Marasco, column 13, middle paragraph; see also column 20, paragraph 2; see also column 22, second to last paragraph; see also column 29, “Construction and Eukaryotic Expression of F105 Single Chain Antibodies With and Without SEKDEL Endoplasmic Retention Signal” section).

The prior art teachings of Marasco et al. differ from the claimed invention as follows:

For *claim 1*, Marasco et al. fail to teach the introduction of a second library. Marasco only teaches the use of a first heavy chain variable library (e.g., see column 31, lines 44-47, “Using the above-described technique, six mutant sFv105 antibodies were produced in which the amino acids in the CDR 3 region of the heavy chain were replaced by random amino acids”).

However, Waterhouse et al. teach the following limitations that are deficient in Marasco et al.:

For *claim 1*, Waterhouse et al. teach screening libraries of heavy/light chain antibodies that can be “co-selected” to produce antibodies (or fragments) with high affinity (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screen a library of intracellular antibodies as taught by Marasco et al. using two libraries (i.e., a library of heavy and light chains) as taught by Waterhouse et al. because Waterhouse et al. explicitly state that both the heavy and light chain regions can be varied simultaneously (e.g., see Waterhouse, column 1). Furthermore, a person of ordinary skill in the art would have been motivated to use two libraries to increase the affinity of the antibody. For example, Marasco et al. state, “mutants having different binding affinities to the envelope glycoprotein [can be] screened” (e.g., see Marasco et al., columns 31 and 32, Construction and Expression of Mutant Antibodies section; see especially, column 32, lines 40-52 wherein a library of six mutants were screened in COS cells), which demonstrates a need for high affinity antibodies. Furthermore, Waterhouse et al. state that such a need may be fulfilled by screening both the heavy and light chains (e.g., see Waterhouse et al., page 2265, paragraph 2 teaching the advantages of “co-selection” and the use of “large combinatorial” libraries; see also page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing “a light chain repertoire in A and a heavy chain repertoire in B” (i.e., producing two libraries simultaneously). Furthermore, a person of ordinary skill in the art would reasonably have

expected to be successful because both references use pairs of V<sub>H</sub> and V<sub>L</sub> antibody proteins. In addition, the structure/function relationship of antibodies and the molecular biology techniques needed to make said antibodies are well established (i.e., this is not an unpredictable art).

*Response*

5. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants maintain all of their previous arguments and incorporate them in their entirety by reference to the 8/23/06 Response (e.g., see 2/14/07 Response, pages 17-20).

[1] To the extent that Applicants are merely repeating their previous arguments, the Examiner contends that those issues were adequately addressed in the previous office actions, which are incorporated in their entireties herein by reference.

[2] Applicants argue that the cited references do not teach an "intracellular" screening method and cite Dr. Zauderer's 132 declaration in support of this position filed 2/15/07. According to Applicants, as explained by Dr. Zauderer, "Marasco's method first identifies an antibody of interest by traditional extracellular screening methods, then expresses the individual, pre-selected antibody intracellularly as a fragment" (e.g., see 2/14/07 Response, page 20, middle

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paragraph). Applicants go on to state that Waterhouse fails to cure this deficiency because the screening steps set forth therein also are performed extracellularly (e.g., see 2/15/07 Response, pages 20 and 21).

[2] The declaration under 37 CFR 1.132 filed 2/15/07 and corresponding arguments are insufficient to overcome the rejection of claims 1-36, 38-44, 53-57, and 59-65 based upon the 35 U.S.C. § 103(a) rejections as set forth in the last Office action because:

It refers only to the system described in the above referenced application and not to the individual claims of the application. As such the declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

For example, Applicants state, “the cited references do not teach or suggest a method of selecting polynucleotides that encode an intracellular immunoglobulin molecule or fragment thereof, whose expression induces a modified phenotype in a eukaryotic host cell upon binding to an intracellular antigen” (e.g., see 2//14/07 Response, page 19, section (a); see also 2/15/07 Declaration wherein the sentiment is repeated in paragraph 6, “The claimed invention is directed to a screen method to select polynucleotides that encode an antigen-specific intracellular immunoglobulin molecule or fragment thereof by introducing separate libraries of immunoglobulin heavy and light chains or fragments thereof into eukaryotic host cells. Expression of the intracellular immunoglobulin induces a modified phenotype in a eukaryotic host cell by binding to an intracellular antigen”). However, such an induction is not required by the claims. Claim 1, step (a) for example, reads “said population can be induced to exhibit a predetermined modified phenotype”; see also step (d), “permitting expression ... under conditions wherein said modified phenotype can be detected”). That is, the “recovery” step in

claim 1(e) is only triggered upon induction of a predetermined phenotype, which is not required by the claims. Thus, the claims are not necessarily drawn to an “intracellular” screening method as purported. In addition, Applicants’ use of “comprising” language does not preclude additional “extracellular” method steps.

It should also be noted that Applicants have defined “recovery” quite broadly in their specification. For example, paragraph 118 reads, “By ‘recovery’ is meant a crude separation of a desired component from those components which are not desired. For example, host cells are ‘recovered’ based on their detachment from a solid substrate, and polynucleotides of the library are recovered from those cells by crude separation from other cellular components. It is to be noted that the term ‘recovery’ does not imply any sort of purification or isolation away from viral and other components”) (emphasis added). Thus, any expression of said polynucleotides in a eukaryotic host cell and subsequent characterization of the cell lysate will constitute a “recovery” under this broad definition. In the present case, Marasco et al. disclose the collection of a “desired” lysate to analyze the proteins in solution; which could be regarded as a “recovery” step because said lysate contains the DNA. Thus, even if, assuming arguendo, Applicants’ claims were limited to an intracellular screening method (which is not the case, see above), Marasco et al. would still read (in part) on such a method.

Thus, Marasco et al. is not deficient and, as a result, Applicants’ arguments with regard to Waterhouse et al. are moot. Furthermore, Applicants’ arguments do not address the Zauderer et al. and Rowlands et al. references.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

[3] Applicants argue that a person of ordinary skill in the art would not have been motivated to modify or combined the cited references. Applicants state, "As set forth in Applicants' reply of August 23, 2006, a person of ordinary skill in the art would have had absolutely no motivation to modify the screening method of Marasco by introducing a second library of polynucleotides into the cells, as specified in the claims" (e.g., see 2/14/07 Response, page 21, last paragraph).

[3] To the extent that Applicants are merely repeating their previous arguments in the August 23, 2006 office action, the Examiner contends that those issues were adequately addressed in the previous responses thereto, which are incorporated in their entireties herein by reference.

[4] Applicants argue, "The F105 single chain antibody of Marasco contains both a heavy chain variable region and a light chain variable region ... Thus, the F105 single chain antibody – by itself – is capable of binding to the gp120 antigen. Accordingly, a person of ordinary skill in the art would have had no reason to introduce even a single second polynucleotide encoding a second immunoglobulin subunit polypeptide into the cells used in Marasco, much less a library of polynucleotides encoding a plurality of intracellular immunoglobulin subunit polypeptides, as required by the present claims" (e.g., see 2/15/07 Response, paragraph bridging pages 21 and 22).

[4] The Examiner respectfully disagrees. This statement ignores the express teaching in Marasco as pointed out in a previous response (e.g., see Marasco et al., columns 31 and 32, "Mutants having different binding affinities to the envelope glycoprotein [can be] screened").

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Thus, Applicants arguments are moot. See also 11/20/06 Response, page 23, section [4] discussing the “numerical” advantages for using a second library.

[5] Applicants argue, “the Examiner still has not provided any explanation of how the addition of a second library encoding a plurality of second intracellular immunoglobulin subunit polypeptides could possible “increase the affinity” of the single chain antibody of Marasco. Indeed, the addition of an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region to a single chain antibody would not be expected to increase the affinity of the single chain antibody for its antigen” (e.g., see 2/14/07 Response, page 22, middle paragraph).

[5] The Examiner respectfully disagrees. Applicants have misinterpreted the Examiner’s arguments. The above rejection indicates that a “second” library will be introduced into the  $V_L$  region of the ScFv thus forming two libraries i.e., a library of  $V_H$  and a library of  $V_L$ . Co-selection of these two libraries will result in the increased affinity.

[6] Applicants argue, “one of skill in the art actually would have been deterred from using an Fab fragment that contains heavy and light chain constant regions as disclosed in Waterhouse for intracellular expression in Marasco” and cite Marasco at column 20, lines 36-44 in support of this position (e.g., see 2/14/07 Response, bottom of page 22).

[6] The constant regions are not required. The increased affinity results from the co-selection of the  $V_H$  and  $V_L$  libraries. In addition, this represents a “less preferred” embodiment, not a “teaching away” as purported. See MPEP § 2123.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained



6. Claims 1-36, 38-44, 53-57, and 59-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) in view of Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266) (of record) and in further view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) (of record) as evidenced by International Committee on Taxonomy of Viruses. ICTVdb Descriptions: 58. Poxviridae. Retrieved April 18, 2006, pages 1-3 and Wikipedia, the Free Encyclopedia. Poxviridae. Retrieved April 18, 2006, pages 1 and 2.

For *claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62*, Marasco et al. and Waterhouse et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71, 75-79.

For *claim 23*, Marasco et al. teach the use of a plasmid vector (e.g., see column 31, last paragraph; see also figure 3).

The prior art teaching of Marasco et al. and Waterhouse et al. differ from the claimed invention as follows:

For *claim 2-8, 10-20*, Marasco et al. and Waterhouse et al. fail to recite method steps for "biopanning" wherein the polynucleotides are recovered, introduced and expressed again in a population of host cells.

For *claim 22*, Marasco et al. and Waterhouse et al. fail to disclose a multiplicity of

infection (MOI) ranging from about 1 to about 10.

For *claims 33-36*, Marasco et al. and Waterhouse et al. fail to disclose vaccinia. In addition, the references fail to disclose an attenuated vaccinia virus.

For *claims 42-44*, Marasco et al. and Waterhouse et al. fail to disclose the T7 phage and p7.5 promoters.

For *claims 63-65*, Marasco et al. and Waterhouse et al. fail to disclose epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

However, Rowlands et al. and Zauderer et al. teach the following limitations that are deficient in Marasco et al. and Waterhouse et al.:

For *claim 2-8 and 10-20*, the combined references of Rowlands et al. and Zauderer et al. (see entire document) teach biopanning. For example, Zauderer et al. disclose steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity i.e., they use “biopanning” techniques (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, “The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure”). Zauderer et al. disclose “isolating” the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, “The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves

combining isolated fractions]”).

For *claim 22*, the combined references of Rowlands et al. and Zauderer et al. teach an MOI = 1 (e.g., see Zauderer et al., page 86, line 2).

For *claims 33-36*, the combined references of Rowlands et al. and Zauderer et al. teach the use of vaccinia virus including an attenuated form of vaccinia virus (e.g., see Rowlands, page 4, second full paragraph, “It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form”; see also page 6, paragraph 3; see also page 4, paragraph 2; see also page 8, paragraph 1; see also claim 9, “A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter”; see also page 2, middle paragraph, “An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end”; see also Zauderer et al., page 52, lines 13-16, “The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector”; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., page 34, last two paragraphs disclosing “attenuated” viruses).

For *claims 42-44*, the combined references of Zauderer et al. and Rowlands et al. disclose T7 phage promoters. For example, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see Rowlands page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter"; see also claim 6 wherein p7.5k, 11k and 19k are disclosed).

For *claims 63-65*, Zauderer et al. disclose the use of epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to select for a library of both heavy and light intracellular antibody chains as taught by the combined references of Marasco et al. and Waterhouse et al. using a vaccinia virus vector as taught by the combined references of Zauderer et al. and Rowlands et al. because the combined references of Marasco et al. and Waterhouse et al. explicitly state that any vector can be used including poxvirus (e.g., see Marasco et al., column 21, "However, the techniques described can readily be used to introduce the antibody genes into other cells, preferably human cells. For example, using a mammalian expression vector, such as ... pox vector ... These vectors can be used to transduce cells by standard techniques well known to the skilled artisan"; see also middle of column 26), which would include the vaccinia virus disclosed by the combined references of Zauderer et al. and Rowlands et al. (see above). Furthermore, one of ordinary skill in the art would have been motivated to make the vaccinia virus as taught by the combined references of

Zauderer et al. and Rowlands et al. because Zauderer et al. explicitly state that the their “tri-molecular” approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells and Rowlands further indicate that this vector can be used to create fully functional antibodies that can still undergo glycosylation (e.g., see Zauderer et al., page 22, lines 14-17, “Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells”; see also Rowlands et al., page 4, paragraphs 2 and 3, “One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.”). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because the combined references of Zauderer et al. and Rowlands et al. indicate that antibody libraries can be easily generated using a vaccinia virus. Furthermore, the combined references of Marasco et al. and Waterhouse indicate that the use of any vector is “routine” in the art (e.g., see Marasco et al., column 21, “These vectors [pox virus] can be used to transduce cells by standard techniques well known to the skilled artisan”). In addition, Rowlands et al. state, “The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade. Over 75 different virus gene products and a variety of other proteins

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including growth factors, cell surface antigens, oncogenes, bacterial structural proteins and enzymes, and protozoan proteins have been expressed in vaccinia for a variety of purposes [i.e., this is not an unpredictable art]"; see also column 36, paragraph 1 wherein separation of the desired cell lysate is disclosed containing the polynucleotides; see also column 34, line 44 wherein again a separation of the lysate is disclosed, which would constitute a "recovery" step under Applicants' broad definition for the term).

### *Response*

7. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "As explained in detail in Section I.A, above, the rejections of claim ... under 35 U.S.C. § 103 based on Marasco and Waterhouse is in error because not all elements of the claims are taught or suggested by these references, and a person of ordinary skill in the art would not have been motivated to modify or combine the references. Neither Rowlands nor Zauderer cure the deficiencies of Marasco and Waterhouse, and neither reference provide a motivation to modify or combine the cited references to arrive at a method that falls within the scope of the currently presented claims" (e.g., see 2/14/07 Response, pages 17-20).

To the extent that Applicants are merely repeating their previous arguments, the

Examiner contends that those issues were adequately addressed in above sections, which are incorporated in their entireties herein by reference. Furthermore, there are no deficiencies with regard to Marasco and Waterhouse as set forth above and, as a result, Applicants' arguments are moot. In addition, even if, assuming *arguendo*, Waterhouse and Marasco were deficient (which is not the case, see above), the combined references of Zauderer et al. and Rowlands teach the use of "biopanning" techniques that would read on the recovery step denoted in claim 1, step (e) for example.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the vaccinia virus as taught by the combined references of Zauderer et al. and Rowlands et al. because Zauderer et al. explicitly state that their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells and Rowlands further indicate that this vector can be used to create fully functional antibodies that can still undergo glycosylation (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraphs 2 and 3, "One advantage of this system is the authenticity of gene products, particularly those

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requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.”).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

### ***Double Patenting***

8. Claims 1-36, 38-44, 53-57, and 59-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 84-122 of U.S. Patent Application Serial No. 09/987,456 (referred to herein as ‘456) (especially claims 84, 88-92, 96, 97, 99, 103, 107-122) in view of Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) and Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) (of record) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) (of record). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).



For *claim 1*, the '456 application claims discloses a method of selecting polynucleotides which encode an immunoglobulin molecule, or fragment thereof (e.g., see claim 84). In addition, the '456 application discloses providing a population of eukaryotic host cells capable of expressing said immunoglobulin molecule (e.g., see claim 84, step (a)). The '456 application also disclose introducing into said population of host cells a first and second library of polynucleotides, through operable association with a transcriptional control region, a plurality of first intracellular immunoglobulin subunit polypeptides, each comprising a first immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain region (e.g., see claim 84, steps (a)(ii) and (b)(ii)). The '456 application also disclose combining said second intracellular immunoglobulin subunit polypeptide with said first subunit to form a plurality of immunoglobulin molecules (e.g., see claim 84, step (b)). The '456 application also discloses permitting expression of said plurality of immunoglobulins and recovering the polynucleotides of said first library (e.g., see claim 84, step (e)).

For *claims 2-8 and 10-20*, the '456 application also discloses recovering the polynucleotides and permitting them to be expressed multiple times for the purpose of increasing ligands with higher affinity i.e., biopanning (e.g., see claims 88-92).

For *claim 9*, the '456 application discloses human antibodies (e.g., see claims 84, 93, 94, 127, 128 and 131).

For *claims 10-17*, the '456 application discloses both heavy and light constant/variable regions (e.g., see claims 84, 96, 97, 107, 110, 113, 116, 117 and 120).

For *claims 18, 19, 24-35, 38, 39*, the '456 application discloses the eukaryotic

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poxvirus vector including vaccinia (e.g., see claims 84, 88, 89, 90, 92, 107, 108, 109, 110, 111, 112, 114, 115, 118 and 119).

For *claim 22*, the '456 application discloses a multiplicity of infection (MOI) ranging from about 1 to about 10 (e.g., see claim 99)

The '456 application differs from the claimed invention as follows:

For *claim 1*, the '456 application fails to disclose selecting an "intracellular" immunoglobulin whose expression induces a modified phenotype in a eukaryotic cell and permitting expression of said plurality of intracellular immunoglobulins under condition wherein said modified phenotype can be detected.

For *claims 21 and 23*, the '456 application fails to disclose the use of a plasmid vector.

For *claims 36*, the '456 application fails to disclose an attenuated form of vaccinia.

For *claims 40 and 41*, the '456 application fails to disclose various promoters including constitutive promoters.

For *claims 42-44*, the '456 application fails to disclose the T7 phage and p7.5 promoters.

For *claims 53-57*, the '456 application fails to disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen.

For *claims 59-62*, the '456 application fails to disclose heterologous

polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence.

For *claims 63-65*, the '456 application fails to disclose epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

However, Marasco et al., Rowlands et al. and Zauderer et al. teach the following limitations that are deficient in '456:

For *claim 1*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. (see entire documents) teach the intracellular antibodies and their use to induce a phenotypic change by binding to an intracellular antigen (e.g., see figure 3; see also columns 35 and 36, section entitled "Ability of Antibody Envelope Glycoprotein to Inhibit Envelope Protein Biosynthesis And Activity starting on line 16 of column 34 disclosing a modified phenotype, decreased envelope protein biosynthesis, that occurs when the intracellular antibody, sFv105 or sFv105-KDEL, to in COS cells; see also column 8, paragraph 1, "the method of using intracellular antibodies to bind to the newly synthesized gp160 in the lumen of the endoplasmic reticulum and inhibit its transport to the Golgi apparatus, greatly reduces the amount of protein available for cleavage to gp120 and gp41. Accordingly, the viral particles produced have greatly diminished amounts of gp120 and gp41 on their surface. Such particles are not considered as infectious.; see also column 35, last paragraph, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited ... [wherein] sFv105-KDEL specific

binding to the HIV-1 glycoprotein”; see also column 34, “Ability of Antibodies to be Expressed in Mammalian Cells” section; see also column 23, lines 13-17). Thus, the intracellular antibody, sFv105, induces a modified phenotype, change in gp120 biosynthesis and particle infectivity, by binding to an intracellular antigen, gp160; see also Rowlands et al., page 4, paragraphs 2 and 3, “One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.”).

For *claims 21 and 23*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. also disclose the use of a plasmid vector (e.g., see Marasco et al. column 31, last paragraph; see also figure 3).

For *claims 33-36*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. teach the use of vaccinia virus including an attenuated form of vaccinia virus (e.g., see Rowlands, page 4, second full paragraph, “It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form”; see also page 6, paragraph 3; see also page 4,

paragraph 2; see also page 8, paragraph 1; see also claim 9, “A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter”; see also page 2, middle paragraph, “An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end”; see also Zauderer et al., page 52, lines 13-16, “The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector”; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., page 34, last two paragraphs disclosing “attenuated” viruses).

For *claims 40 and 41*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose various promoters including constitutive promoters (e.g., Marasco et al., column 21, paragraphs 1 and 2).

For *claims 42-44*, the combined references of Marasco et al., Zauderer et al. and Rowlands et al. disclose the p7.5 and T7 phage promoters (e.g., see Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, “Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter”; see also claim 6 wherein p7.5k, 11k and 19k are disclosed).

For *claims 53-57*, the combined references of Marasco et al., Rowlands et al. and

Zauderer et al. disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen (e.g., see Marasco et al., column 9, second to last paragraph, “intracellular expression of an antibody to its target, for example, the antibody to the [HIV] envelope glycoprotein ... results in an antibody that binds the target, e.g. envelope glycoprotein ... and prevents further processing ... One could even have the antibody under the control of a promoter that will be specifically activated by the target (e.g. an HIV LTR) thereby only turning the antibody on when the target is present”; see also column 8, paragraph 3, “Syncytium formation is mediated solely by the HIV-1 envelope protein expressed on the infected cell surface”; see also columns 37-39 and figures 9-12).

For *claims 59-62*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence (e.g., see Marasco, column 16, last paragraph wherein localization sequences are disclosed; see also column 33, line 40; see also column 13, line 40 wherein KDEL is disclosed). Furthermore, Marasco teaches localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody (e.g., see Marasco, column 13, middle paragraph; see also column 20, paragraph 2; see also column 22, second to last paragraph; see also column 29, “Construction and Eukaryotic Expression of F105 Single Chain Antibodies With and Without SEKDEL Endoplasmic Retention Signal” section).

For *claims 63-65*, Zauderer et al. disclose the use of epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies disclosed by the '456 application using intracellularly expressed and/or localized antibodies as taught by the combined references of Marasco et al., Rowlands et al. and Zauderer et al. because Marasco et al., for example, explicitly state that pox virus can be used to express intracellular antibodies (e.g., see Marasco column 26, lines 43-46, "Other mammalian expression vectors such as herpes virus expression vectors, or pox virus expression vectors can also be used"), which would encompass the vaccinia virus disclosed by the '456 application. Furthermore, Rowlands et al. further indicate that this vector can be used to create fully functional antibodies that can still undergo glycosylation which is advantageous for mammalian processing (e.g., see Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin."). Finally, a person of ordinary skill in the art would reasonably have expected to be successful because Rowlands et al. teach that antibodies can easily be expressed in vaccinia virus (e.g., see Rowlands et al., page 4, paragraph 3, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant

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antibody which is secreted into the medium and can thus be recovered in functional form.”). Furthermore, Marasco et al. indicate that the use of any vector is “routine” in the art (e.g., see Marasco et al., column 21, “These vectors [pox virus] can be used to transduce cells by standard techniques well known to the skilled artisan”). In addition, Rowlands et al. state, “The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade. Over 75 different virus gene products and a variety of other proteins including growth factors, cell surface antigens, oncogenes, bacterial structural proteins and enzymes, and protozoan proteins have been expressed in vaccinia for a variety of purposes [i.e., this is not an unpredictable art]”).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### *Response*

9. Applicant’s arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants’ newly amended and/or added claims and/or arguments.

Applicants request that the double patenting rejection with regard to the ‘456 application be held in abeyance until the remaining issues are resolved (e.g., see 2/15/07 Response, page 24, last paragraph).

The provisional rejection will not be held in abeyance (e.g., see MPEP § 804 B. Between



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Copending Applications—Provisional Rejections, “The ‘provisional’ double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that “provisional” double patenting rejection is the only rejection remaining in one of the applications.”). Here, a double patenting rejection is NOT the only rejection remaining in one of the applications and thus the double patenting rejection is proper.

Accordingly, the double patenting rejection cited above is hereby maintained.

10. Claims 1-36, 38-44, 53-57, and 59-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-128 of U.S. Patent Application Serial No. 10/465,808 (referred to herein as ‘808) in view of Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) and Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) (of record) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) (of record). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

For *claim 1, 10-17*, the ‘808 application discloses a method for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule

(e.g., see '808, claim 46). The '808 application also discloses introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity (e.g., see claim 46, step (a); see also claim 80 disclosing the use of mammalian host cells which would inherently be permissive for vaccinia virus infectivity). The '808 application also discloses a first library of polynucleotides encoding through operable association with a transcriptional control region, a plurality of first immunoglobulin subunit polypeptides (e.g., see '808 application, claim 46, step (a); see also claims 59 and 68 disclosing constant heavy chain region; see also claims 128). In addition, the '808 application discloses each first immunoglobulin subunit polypeptide comprising a first immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region (e.g., see '808, claim 46 claim 128, step (a)(i); see also claims 59, 60, 61, 62, 63, 66, 67, 68, 70 and 98 disclosing use of "heavy" chains). The '808 application also discloses an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region wherein said variable region corresponds to said first constant region (e.g., see '808, claim 46(a)(ii); see also claims 69, 70, 71 and 99 disclosing the use of "light" chains). The '808 application also discloses introducing into said host cells a second library of polynucleotides encoding through operable association with a transcriptional control region a plurality of second immunoglobulin subunit polypeptides each comprising (e.g., see '808, claim 46(b); see also claim 80). In addition, the '808 application discloses a second immunoglobulin constant region selected from the group consisting of a heavy chain constant region or a

light chain constant region wherein said second immunoglobulin constant region is not the same as said first immunoglobulin constant region (e.g., see '808, claim 46(b)(i)). The '808 application also discloses an immunoglobulin variable region selected from the group consisting of heavy chain variable region and a light chain variable region, wherein said variable region corresponds to said second constant region (e.g., see '808, claim 46(b)(ii)). The '808 also discloses said second immunoglobulin subunit polypeptide that is capable of combining with said first immunoglobulin polypeptide to form an immunoglobulin molecule (e.g., see claim 46(b)(iii)). Finally, the '808 application teaches permitting expression of immunoglobulin molecules, contacting said immunoglobulin molecules with an antigen, and recovering polynucleotides of said first library from those individual host cells which exhibit said modified phenotype (e.g., see claim 46, steps (c)-(e)).

For *claims 2-8 and 20*, the '808 application discloses repetitive steps for "biopanning" a library (e.g., see '808, 48, 52, 115 and 123).

For *claim 9*, the '808 application discloses human antibodies (e.g., see claim 58).

For *claims 18, 19, 20, 24-35, 38, 39*, the '808 application discloses the eukaryotic poxvirus (e.g., see claims 85-88, 94 and 95).

For *claim 22*, the '808 application discloses a multiplicity of infection (MOI) ranging from about 1 to about 10 (e.g., see claim 76).

For *claims 40-44*, the '808 application discloses various promoters including T7 phage and p7.5 (e.g., see claims 92-96).

The '808 differs from the claimed invention as follows:

For *claim 1*, the '808 application fails to disclose selecting an "intracellular" immunoglobulin whose expression induces a modified phenotype in a eukaryotic cell and permitting expression of said plurality of intracellular immunoglobulins under condition wherein said modified phenotype can be detected. The '808 application also fails to disclose the single chain embodiment described, for example, in claim 69.

For *claims 21 and 23*, the '808 application fails to disclose the use of a plasmid vector.

For *claims 36*, the '808 application fails to disclose an attenuated form of vaccinia.

For *claims 53-57*, the '808 application fails to disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen.

For *claims 59-62*, the '808 application fails to disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence.

For *claims 63-65*, the '808 application fails to disclose epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

However, Waterhouse, Rowlands et al., and Zauderer et al. teach the following limitations that are deficient in Marasco et al.:

For *claim 1*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. (see entire documents) teach the use of intracellular antibodies including the induction of a phenotypic change by binding to an intracellular antigen (e.g., see figure 3; see also columns 35 and 36, section entitled "Ability of Antibody Envelope Glycoprotein to Inhibit Envelope Protein Biosynthesis And Activity starting on line 16 of column 34 disclosing a modified phenotype, decreased envelope protein biosynthesis, that occurs when the intracellular antibody, sFv105 or sFv105-KDEL, to in COS cells; see also column 8, paragraph 1, "the method of using intracellular antibodies to bind to the newly synthesized gp160 in the lumen of the endoplasmic reticulum and inhibit its transport to the Golgi apparatus, greatly reduces the amount of protein available for cleavage to gp120 and gp41. Accordingly, the viral particles produced have greatly diminished amounts of gp120 and gp41 on their surface. Such particles are not considered as infectious.; see also column 35, last paragraph, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited ... [wherein] sFv105-KDEL specific binding to the HIV-1 glycoprotein"; see also column 34, "Ability of Antibodies to be Expressed in Mammalian Cells" section; see also column 23, lines 13-17). Thus, the intracellular antibody, sFv105, induces a modified phenotype, change in gp120 biosynthesis and particle infectivity, by binding to an intracellular antigen, gp160; see also Rowlands et al., page 4, paragraphs 2 and 3, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be

used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.”).

For *claims 21 and 23*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. also disclose the use of a plasmid vector (e.g., see Marasco et al. column 31, last paragraph; see also figure 3).

For *claims 33-36*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. teach the use of vaccinia virus including an attenuated form of vaccinia virus (e.g., see Rowlands, page 4, second full paragraph, “It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form”; see also page 6, paragraph 3; see also page 4, paragraph 2; see also page 8, paragraph 1; see also claim 9, “A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter”; see also page 2, middle paragraph, “An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end”; see also Zauderer et al., page 52, lines 13-16, “The high yield of viral recombinants in tri-molecular

recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., page 34, last two paragraphs disclosing "attenuated" viruses).

For *claims 53-57*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen (e.g., see Marasco et al., page 9, second to last paragraph, "intracellular expression of an antibody to its target, for example, the antibody to the [HIV] envelope glycoprotein ... results in an antibody that binds the target, e.g. envelope glycoprotein ... and prevents further processing ... One could even have the antibody under the control of a promoter that will be specifically activated by the target (e.g. an HIV LTR) thereby only turning the antibody on when the target is present"; see also page 8, paragraph 3, "Syncytium formation is mediated solely by the HIV-1 envelope protein expressed on the infected cell surface"; see also paragraph bridging pages 37-39 and figures 9-12). The '808 application discloses an altered susceptibility to HIV infection (e.g., see column 23, paragraph 2).

For *claims 59-62*, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence (e.g., see Marasco, column 16, last paragraph wherein localization sequences are

disclosed; see also column 33, line 40; see also column 13, line 40 wherein KDEL is disclosed). Furthermore, Marasco teach localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody (e.g., see Marasco, column 13, middle paragraph; see also column 20, paragraph 2; see also column 22, second to last paragraph; see also column 29, "Construction and Eukaryotic Expression of F105 Single Chain Antibodies With and Without SEKDEL Endoplasmic Retention Signal" section).

For *claims 63-65*, Zauderer et al. disclose the use of epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies disclosed by the '808 application using intracellularly expressed and/or localized antibodies as taught by the combined references of Marasco et al., Rowlands et al. and Zauderer et al. because Marasco et al., for example, explicitly state that pox virus can be used to express intracellular antibodies (e.g., see Marasco column 26, lines 43-46, "Other mammalian expression vectors such as herpes virus expression vectors, or pox virus expression vectors can also be used"), which would encompass the vaccinia virus disclosed by the '808 application (e.g., see '808 application, claims 85-88). Furthermore, Rowlands et al. further indicate that this vector can be used to create fully functional antibodies that can still undergo glycosylation which is advantageous for mammalian processing (e.g., see Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such



as glycosylation. This may be particularly important for genes of mammalian origin.”), which is a preferred embodiment of the ‘808 application (e.g., see ‘808 application, claims 58 and 80). Finally, a person of ordinary skill in the art would reasonably have expected to be successful because Rowlands et al. teach that antibodies can easily be expressed in vaccinia virus (e.g., see Rowlands et al., page 4, paragraph 3, “It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.”). Furthermore, Marasco et al. indicate that the use of any vector is “routine” in the art (e.g., see Marasco et al., column 21, “These vectors [pox virus] can be used to transduce cells by standard techniques well known to the skilled artisan”). In addition, Rowlands et al. state, “The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade. Over 75 different virus gene products and a variety of other proteins including growth factors, cell surface antigens, oncogenes, bacterial structural proteins and enzymes, and protozoan proteins have been expressed in vaccinia for a variety of purposes [i.e., this is not an unpredictable art]”).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response***

11. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue request that the rejection be held in abeyance and note MPEP §804.1.A.1

The provisional rejection will not be held in abeyance (e.g., see MPEP § 804 B. Between Copending Applications—Provisional Rejections, "The 'provisional' double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications."). Here, a double patenting rejection is NOT the only rejection remaining in one of the applications and thus the double patenting rejection is proper. Applicants citation (e.g., see 2/14/07 Response, page 25) only serves to confirm this position.

Accordingly, the double patenting rejection cited above is hereby maintained.

***Conclusion***

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37

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CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

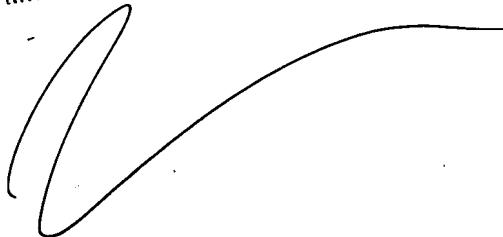
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.  
May 8, 2007

JON EPPERSON  
PRIMARY EXAMINER

A handwritten signature in black ink, consisting of a large, stylized 'J' followed by a horizontal line extending to the right.